Remarks

Claims 1-9, 12-19 and 29-33 are pending in the subject application. By this Amendment, Applicants have canceled claims 13-15 and 29-31, amended claims 1, 3, 6, 17 and 32 and added new claims 34-42. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed (see, for example, pages 24-25 and the original claims of the application). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-9, 12, 16-19 and 32-42 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants request, at the time the Examiner considers this response, the courtesy of an interview to discuss the issues in this application.

Claim 1 is objected to for informalities. The Office Action indicates the term "(a)" is a typographical error. Applicants gratefully acknowledge the Examiner's careful review of the claims. Applicants have replaced the term "(a)" with "a" in claim 1. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 3-6, 17, 18 and 32 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully assert that the claims as filed are definite and have addressed the rejections separately.

The phrases "said mutagenizing comprising exchanging Gly192" and "said mutagenizing comprising exchanging Arg208" in claim 32 is vague and renders the claim indefinite. The term "comprising" is an open language that implies some other element is intended. It is unclear what other "mutagenizing" is intended in the claim. Applicants have amended the claim and believe that this issue is now moot. However, should the Examiner find the amendments made in this regard unsatisfactory, Applicants would appreciate an opportunity to discuss and resolve any remaining issues.

The term "and/or" in line 4 of claim 3 is vague and renders the claim indefinite. It is unclear what is intended. Changing the term "and/or" to " ... or. .. or both" would be remedial. Claims 4 and 5 depend from claim 3. In accordance with the Examiner's suggestion, claim 3 has been amended in a manner that clarifies the claim.

The phrase "additional (functional) domains" of claim 6 is vague and renders the claim indefinite. It is unclear whether the term "(functional)" is intended in the claim. Removing the parenthesis would be remedial. In accordance with the Examiner's suggestion, claim 6 has been amended to removal of the word "functional" in parenthesis.

The phrase "alternative domains" of claim 6 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "alternative domains". Applicants have amended claim 6 to delete the phrase "alternative domains" and replace it with "exchanging domains having the same function" to add greater clarity to the claim.

The term "MDM2" in claim 17 is vague and renders the claim indefinite. The term "MDM2" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claim. Claim 18 depends from claim 17. By this Amendment, Applicants have replaced the abbreviation "MDM2" with "Murine Double Minute 2" and then placed the abbreviation in parenthesis. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 1-9, 12-19 and 29-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a TCR complex wherein the alpha- and beta-chains of an MDM2(81-88)-specific TCR are used as alpha-chain and beta-chain, and wherein the Gly192 of the constant region of the alpha-chain and the Arg208 of the constant region of the beta-chain are exchanged by Arg 192 in the constant region of the alpha-chain and by Gly208 in the constant region of the beta-chain, does not reasonably provide enablement for a method, in vitro or in vivo, for producing any other heterodimeric specific wildtype or chimeric TCR having any antigen specificity, wherein glycine, serine, threonine, valine, or alanine is introduced after the mutagenesis of the DNA molecule that introduces the sterically recessed group including Arg208, and glutamine, glutamic acid, alpha-methylvaline, histidine, hydroxylysine, tryptophan, lysine, arginine, phenylalanine or tyrosine is introduced after the mutagenesis of the DNA molecule that introduces the sterically projecting group including Gly192. Applicants respectfully assert that the claims as filed are enabled.

In citing and analyzing the Wands factors, the Examiner has concluded that there would be undue experimentation in order for one skilled in the art to make and use the claimed invention.

First, the Examiner seems to require that in order to practice the claimed invention, the skilled person needs to "completely understand the triggering mechanisms of the receptors" (citing Khuns, page 8). Applicants submit that this position is in error as the law does not require one skilled in the art to know "why" inventions work. Rather, the law requires that the specification teach how to make and use the claimed invention.

Further, the disclosure gives specific guidance *where* the mutations shall be located and what functions they have (namely, steric functions). Applicants further note that the claims indicate that the mutations are to be made at amino acid-surfaces in the TCR constant domain. It is clear that these mutations are put into places where the actual biological function of the TCR would not be disturbed. The Office Action also argues that amino acid mutations can have effects on the function of a protein (referring to the situation in, *e.g.*, EGF, which is not a TCR at all), and that knowing the amino acid sequence would not tell about the function (citing Skolnick, page 9). Applicants acknowledge that amino acid changes (mutations) can lead to changes in the biological function of a protein, but this is not true for all mutations. The substitution of similar amino acids often does not lead to changes in biological function. Regarding the reliance on Skolnick for the proposition that undue experimentation is required to practice the claimed invention, Applicants submit that the reference fails to support the Patent Office's position in this matter. In the present case, the structure/function of the altered polypeptides is well-known in the art and TCR have been extensively studied.

The Examiner also stated that different TCRs derived from different species would have different amino acids, and thus claims 32 and 33 would be (basically) confusing, if no Gly or Arg would be present (page 10). Applicants submit that TCRs, in their constant domains, are highly conserved, and thus most TCR constant domains have sequence homologies of over 95%. Additionally, Applicants submit that a standardized and dedicated numbering and homology system existed for TCR (and other proteins of the immune system), rendering this concern moot (see, for example, the print-out from the ImMunoGeneTics Information System which provides evidence that the database has been in existence since about 1989).

Applicants further submit that evidence regarding the broad applicability of the claimed method has been presented in this matter (see Voss *et al.*, Reference R3 in the IDS considered by the Examiner on September 19, 2009). In that reference, the authors state (see Abstract):

> We mutated the two residues so as to invert the sense of this interaction analogous to a charged "hole-into-knob" configuration. We show that this inversion in the CαCβ interface promotes selective assembly of the introduced TCR while preserving its specificity and avidity for Ag ligand. Noteworthily, this TCR modification was equally efficient on both a Mu and a Hu TCR. Our data suggest that this approach is generally applicable to TCR independently of their Ag specificity and affinity, subset distribution, and species of origin.

In detail, Voss *et al.* not only tested the MDM2 receptor of the invention, but also developed a gp100 receptor. These two receptors show that "the reciprocal mutation approach may be generalized to tumor-reactive TCR with a broad range of Ag affinities" (page 400, right column, second to last paragraph). Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

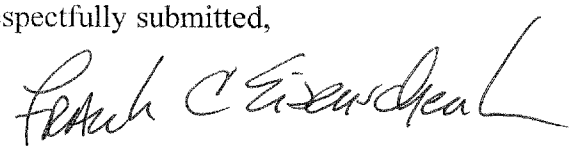
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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IMGT®, the international ImMunoGeneTics information system® http://www.imgt.org, is a high-quality integrated knowledge resource specialized in the immunoglobulins (IG), T cell receptors (TR), major histocompatibility complex (MHC), immunoglobulin superfamily (IgSF), major histocompatibility complex superfamily (MhcSF) and related proteins of the immune system (RPI) of human and other vertebrate species, created in 1989 by Marie-Paule Lefranc (Université Montpellier 2, CNRS). IMGT, a European project since 1992, works in close collaboration with EBI. IMGT consists of sequence databases (IMGT/LIGM-DB, a comprehensive database of IG and TR from human and other vertebrates, with translation for fully annotated sequences, IMGT/MHC-DB, IMGT/PRIMER-DB), genome database (IMGT/GENE-DB), structure database (IMGT/3Dstructure-DB), and monoclonal antibodies database, **Web resources** and **interactive tools**. The IMGT Home page http://www.imgt.org (Montpellier, France) provides a common access to all Immunogenetics data.

IMGT founder and director: Marie-Paule Lefranc (Marie-Paule.Lefranc@igh.cnrs.fr), Université Montpellier 2, CNRS, LIGM, IGH, IFR3, Montpellier (France)

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IMGT databases

- **IMGT/LIGM-DB** LIGM, Montpellier, France
 Nucleotide sequences of IG and TR from 252 species (**141 758 entries**)
- **IMGT/MHC-DB** ANRI, BPRC, hosted at EBI
 Sequences of the human MHC
- **IMGT/PRIMER-DB** LIGM, Montpellier, France
 Oligonucleotides (primers) of IG and TR from 11 species (**1 864 entries**)

- **IMGT/GENE-DB** LIGM, Montpellier, France
 International nomenclature for IG and TR genes from human, mouse, rat and rabbit (**2 224 genes, 3 251 alleles**)

- **IMGT/3Dstructure-DB** LIGM, Montpellier, France
 3D structures (IMGT Colliers de Perles) of IG antibodies, TR, MHC and RPI (**1 786 entries**)
 Source: PDB, INN

IMGT Web resources

- **IMGT Repertoire** (IG and TR, MHC and RPI)
- **IMGT Index** (FactsBook)
- **IMGT Scientific chart** (Sequence description, Numbering, Nomenclature, Representation rules)
- **IMGT Bloc-notes** (Interesting links, PubMed, Meeting announcements, Postdoctoral positions and jobs, Messages, Search engines...)

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- **The IMGT Immunoinformatics page**

- **IMGT/mAb-DB** LIGM, Montpellier, France NEW!
 Monoclonal antibodies (IG, mAb) and fusion proteins for immune applications (FPIA) (**345 entries**)

IMGT tools

- **IMGT/V-QUEST** (sequence alignment software for IG, TR and HLA)
- **IMGT/JunctionAnalysis** (for human and mouse IG and TR)
- **IMGT/Allele-Align**
- **IMGT/PhyloGene**
- **IMGT/DomainDisplay** (Amino acid sequences)

- **IMGT/LocusView, IMGT/GeneView, IMGT/GeneSearch, IMGT/CloneSearch** (for human IGK, IGL, IGH, TRA/TRD, TRB, TRG, mouse TRA/TRD and human MHC)
- **IMGT/GeneInfo** (TIMC and ICH, Grenoble; LIGM, Montpellier)
- **IMGT/GeneFrequency**

- **IMGT/DomainGapAlign**
- **IMGT/Collier-de-Perles**
- **IMGT/DomainSuperimpose**
- **IMGT/StructuralQuery**

IMGT other accesses

- IMGT Other accesses (ARSA, SRS, MRS)
- Compare your sequence against IMGT (BLAST, FASTA)
- IMGT/LIGM-DB Sequence submission
- IMGT flat file release information

IMGT Latest news

- IMGT/mAb-DB is on-line (Fri, 04 Dec 2009 14:54:38 GMT)
- New release of IMGT/3Dstructure-DB (Version 4.0.0) (Thu, 3 Nov 2009 09:10:00 GMT)
- New release of IMGT/V-QUEST (Version 3.2.8) (Mon, 01 Sept 2009 11:22:54 GMT)
- IMGT® celebrates ten years of HONourable behaviour (Thu, 2 Apr 2009 09:24:44 GMT)

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